Optimizing Clozapine Treatment

Dieter Naber, M.D.

Compliance with conventional antipsychotic medication is often poor, with many patients discontinuing treatment only a few months after commencing therapy. The side effects of treatment, which are not necessarily restricted solely to motor symptoms, are often considered to be responsible for this noncompliance. In contrast to conventional antipsychotics, clozapine is associated with only minimal extrapyramidal symptoms, and in most patients, its use results in significant improvements in compliance. However, clozapine does induce a variety of adverse effects, most of which are of limited duration and either preventable or manageable if a number of simple clinical procedures are followed. Clozapine therapy is associated with a beneficial risk/benefit ratio in the majority of treatment-resistant schizophrenic patients. With careful hematologic control, the risk of agranulocytosis can be minimized. The marked increase in the well-being of patients receiving clozapine should stimulate psychiatrists to broaden its use and not limit it to severely treatment-resistant individuals.

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The benefits of antipsychotic therapy for the treatment of schizophrenia are beyond doubt. However, while widely prescribed, these drugs are not universally welcomed by the patients who benefit most from their pharmacologic effects. Indeed, most patients tend to discontinue treatment within a few months of the commencement of therapy. This poor compliance often results from an unacceptable level of side effects.[1] Indeed, acute extrapyramidal symptoms (EPS) are a common phenomenon with conventional antipsychotics[2–4] and are frequently associated with compliance issues.[5] It would be inappropriate to hold EPS solely accountable for the high degree of noncompliance, since subtle emotional and affective restrictions also play an important role; both conditions are strong indications for prescribing atypical antipsychotic therapy. Symptoms of "pharmacogenic anhedonia," "akinetic depression," or "neuroleptic-induced deficit syndrome" are barely measurable on objective rating scales and are difficult to differentiate from the negative symptoms of schizophrenia, but clozapine therapy appears to be particularly beneficial in these patients.

Data collected over the past 30 years at the University of Munich have shown that clozapine use is associated with a considerable feeling of well-being among patients receiving treatment; this is often in stark contrast to the picture experienced by patients receiving conventional antipsychotic therapy immediately prior to switching to clozapine. These observations are applicable to a wide range of patients and are not restricted to those with debilitating motor side effects. To evaluate these findings further, a self-rating scale was developed to assess subjective well-being in patients receiving antipsychotic therapy.[6] The resultant data indicated that this scale was a useful tool for investigating a hitherto neglected psychopathologic dimension. Patients treated with clozapine because of either treatment resistance or intolerable side effects, despite the apparent negative selection, rated their subjective well-being as significantly better than those receiving conventional antipsychotics across a broad band of subscores (Figure 1). These results confirmed our clinical observations and in many ways were similar to the statistically significant, and clinically relevant, improvements in quality of life ratings reported by Meltzer et al.[7] when assessing the impact of clozapine therapy over a 6-month period on 38 patients with treatment-resistant schizophrenia.

The initial step that therefore needs to be taken in terms of optimizing antipsychotic therapy is the routine prescription of clozapine in place of conventional antipsychotics.

UNWANTED ADVERSE EFFECTS OF CLOZAPINE

If clozapine is to be routinely prescribed, then it is important that the incidence of any unwanted side effects is kept to an absolute minimum. Although clozapine has a high therapeutic index (the ratio of clinical benefit to adverse effect), it is associated with a range of adverse effects in most patients.[8,9] However, the majority of these side effects are temporary, preventable, and tolerable as well as being readily manageable.

From the Psychiatrische und Nervenklinik, Universität Hamburg, Germany.

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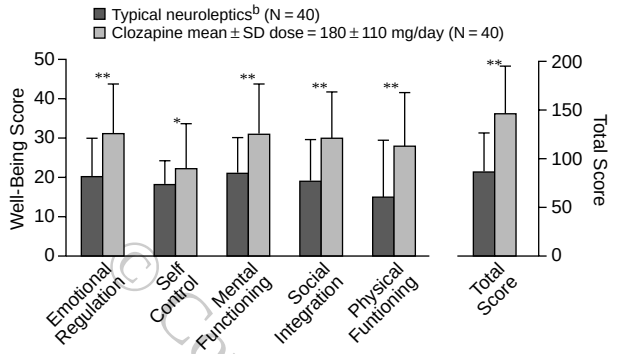
Reprint requests to: Dieter Naber, M.D., Psychiatrische und Nervenklinik, Universitäts-Krankenhaus-Eppendorf, Universität Hamburg, Martinistrasse 52, D-20247 Hamburg, Germany.

Figure 1. Self-Rated Well-Being With Clozapine Treatment[a]



[a]Adapted from reference 6, with permission.
[b]195 ± 110 mg/day chlorpromazine equivalents (haloperidol and flupenthixol).
*p < .05 (t test). **p < .02 (t test).

Table 1. Incidence of Side Effects During Clozapine Inpatient Treatment (N = 480)[a]

	Severity Score (% Incidence)			
Side Effects	All	Mild[b]	Moderate[c]	Severe[d]
EEG alterations	34.4	27.4	6.6	0.4
Fatigue	27.2	12.9	12.9	1.4
Increase in liver enzymes	20.9	15.3	4.7	0.9
Postural hypotension	17.4	11.0	5.2	1.2
Tachycardia	13.8	11.1	2.5	0.2
Leukocytosis	13.5	10.3	3.2	0
Weight gain	13.0	7.1	4.1	1.8
ECG alterations	9.9	5.3	2.6	2.0
Fever	8.8	4.9	3.0	0.9
Hypersalivation	8.0	2.3	4.7	1.0
Obstipation/ileus	7.5	5.4	1.9	0.2
Nausea/vomiting	6.6	4.7	1.7	0.2
Delirious states	4.3	0.9	2.5	0.9
Dermatological effects	1.2	0.4	0.8	0
Leukopenia	0.6	0	0	0.6
Seizure	0.2	0	0	0.2

[a]From reference 10. Abbreviations: ECG = electrocardiogram, EEG = electroencephalogram.
[b]No consequences or no further increase in clozapine dosage or delayed increase in clozapine dosage.
[c]Necessitated a reduction in clozapine dosage.
[d]Withdrawal of clozapine therapy.

A retrospective medical chart review of 640 schizophrenic inpatients at the University of Munich showed that 27% of these patients experienced no side effects whatsoever, while the majority of patients experienced 1 (23%), 2 (24%), or 3 (14%) events.[10] Table 1 lists the incidence and severity of the most frequently reported effects. Electroencephalogram (EEG) alterations, fatigue, increases in liver enzymes, postural hypotension, tachycardia, leukocytosis, and weight gain were diagnosed most frequently. On careful examination, it immediately becomes apparent that the overwhelming majority of these events are either tolerable or manageable. Increases in liver enzymes and fever were events typically reported within the initial 2 to 3 weeks of clozapine therapy; neither usually proved to be of any consequence. Fatigue and weight gain are perhaps the 2 major problems associated with longer term treatment, although both events illustrate a clear dose-dependent effect. No case of agranulocytosis was reported in this series of patients, and only 3 patients were diagnosed with clinically relevant leukopenia.

The antipsychotic efficacy of clozapine was also evaluated in this cohort. Clozapine was administered to patients with either treatment-resistant schizophrenia or intolerable side effects at a mean daily dose of 230 mg during the 7-week observation period. In comparison with standard clozapine doses in the United States, this may appear somewhat on the low side, but it needs to be considered in light of mean European daily doses, which tend not to exceed 250 to 300 mg. It should also be noted that clozapine is prescribed in up to 40% of schizophrenic patients in certain German hospitals; as a result, different selection factors are obviously employed in comparison with the United States. In terms of efficacy, 11% of the sample showed a worsening or no change, 32% demonstrated a slight improvement, 53% a marked improvement, and 4% an almost complete absence of symptoms. At the time of discharge, 60% of patients were receiving treatment solely with clozapine, while a further 21% were receiving clozapine in conjunction with a conventional antipsychotic. Clozapine therapy had been discontinued in the remaining 19% of patients; in 8% this was the result of side effects, while in 6% of patients, psychiatrists reported inadequate efficacy, with 4% reporting noncompliance. A small group of psychiatrists refused to prescribe clozapine to the final 1% because of the drug's association with agranulocytosis. This group of psychiatrists would be advised to consider carefully the proven benefits of clozapine on tardive dyskinesia and suicidality before ruling out such treatments in the future.

COMPLIANCE WITH CLOZAPINE THERAPY

Numerous studies, conducted in both Europe and the United States,[10–14] have indicated a high degree of compliance in patients receiving clozapine, with figures reported to be as high as 90%.[10] In most, if not all, cases, compliance is significantly improved with clozapine when compared with previous conventional antipsychotics.

The wisdom of informing patients about potential side effects is often debated. However, in our experience, most patients will show an increased tolerance of side effects if adequate information regarding the risks and benefits of treatment has been made available to them beforehand. This tolerance serves as a further factor in improving patient compliance.[1] This is true for all antipsychotic therapies, not just clozapine. However, as a result of the mandatory monitoring of white blood cell counts for patients receiving

Table 2. Management of Typical Unwanted Effects of Clozapine Therapy

Side Effect	Incidence (%)	Management
Fatigue[a,b]	8–60	Stimulants (?)
Hypersalivation[b]	6–60	Pirenzepine
EEG alteration	7–50	Reduced dosage
Tachycardia[b]	5–40	β-Blocker
Hypotension[a]	2–30	Sympathomimetic
Weight gain	2–20	Dietary education
Constipation[a]	2–16	Fiber diet
ECG changes	1–30	ECG monitoring
Seizure[b]	0.5–4	Anticonvulsants
Agranulocytosis	0.7–0.9	Withdrawal

[a]Slow titration recommended.
[b]Dose-dependent.

clozapine, these patients are usually extremely well-informed of both the efficacy and safety profiles of the drug.

COMBINATION OF CLOZAPINE WITH CONVENTIONAL ANTIPSYCHOTICS

Combination therapy of clozapine and conventional high-potency antipsychotics, such as haloperidol, has been shown to be effective in cases where the tolerability of clozapine has been limited as a result of either sedation or hypotension. In such cases, clozapine could be administered at a 150-mg daily dose (a dose that would not induce sedation) in conjunction with 2 mg of haloperidol (a dose too low to induce clinically relevant motor side effects).

OPTIMIZING CLOZAPINE TREATMENT

Most of the side effects seen in association with clozapine therapy are of limited duration and are either preventable or manageable if a number of simple clinical procedures are followed.

When commencing treatment, a gradual increase in clozapine dosage considerably reduces the frequency of sedation, hypotension, delirious states, and other effects related to clozapine's anticholinergic properties. In Europe, the recommended titration regimen yields a 200-mg/day dose by the end of week 2 (day 1, 12.5 mg; days 2–4, 25–50 mg; days 5–7, 50–100 mg; days 8–14, 100–200 mg), increasing to 400 mg by the end of week 3 (days 15–21, 200–400 mg) and 600 mg 1 week later (days 22–28, 400–600 mg). By adopting gradual titration, it has been possible to minimize the incidence of many adverse events. Again, data from the University of Munich can be used to support these claims. Fifty-two patients from the earlier cohort discontinued treatment with clozapine because of severe side effects. As there was a strong indication to recommence treatment with clozapine 7–14 days later, an even more gradual titration was adopted (with a 200-mg daily dose targeted by weeks 3–4). Tolerability was much improved as a result, and treatment needed to be withdrawn in only 8 patients (15%).[10]

MANAGEMENT OF TYPICAL UNWANTED EFFECTS (TABLE 2)

Fatigue

A number of case reports from the United States have suggested that using stimulants may be beneficial in cases of fatigue.[15] In contrast, in Europe there is a reluctance to prescribe stimulants to patients with schizophrenia, although this approach could be successfully applied to patients with extreme sedation.

Sialorrhea

Hypersalivation often occurs during the initial 5 to 6 weeks of treatment and, although disturbing, can be markedly reduced by prescribing pirenzepine, a peripheral histamine blocker, or an anticholinergic.

EEG Alterations

Alterations to EEGs will usually improve following dose reduction; in most cases, the prescription of an anticonvulsant would be considered unnecessary.

Tachycardia and Hypotension

Tachycardia and hypotension can be minimized with the coadministration of β-blockers and sympathomimetic drugs, respectively.

Gastrointestinal Symptoms

Gastrointestinal symptoms, predominantly weight gain and constipation, can be effectively managed by dietary education and the adoption of high-fiber diets in the majority of patients. Weight gain appears to be a particular problem in young men, who tend not to be the ideal candidates for dietary education; in these cases, it is sometimes worth considering administering other atypical antipsychotics.

Seizures

Factors that appear to increase the likelihood of seizures include high doses of clozapine, rapid dose titration, the concurrent use of other epileptogenic agents, and a previous history of neurologic abnormalities. In patients in whom seizures are reported, the administration of an anticonvulsant will tend to lead to successful resolution of the problem.

Clozapine therapy is associated with a beneficial risk/benefit ratio in the majority of treatment-resistant schizophrenic patients. Given the careful control of hematologic and other variables, the risk of agranulocytosis or other serious complications is very low.

CONCLUSIONS

Relevant motor side effects and emotional restrictions in association with conventional antipsychotic therapy are

strong indications for the use of clozapine or other atypical antipsychotics. While clozapine does not induce motor side effects, its use is associated with a number of adverse events, the majority of which are preventable by either adopting a gradual increase in clozapine dosage or by following a number of simple routine clinical procedures.

The marked increase in the well-being and quality of life of schizophrenic patients receiving clozapine, a difference that is both statistically significant and clinically relevant, should stimulate psychiatrists to broaden their prescribing of this atypical antipsychotic to the majority of schizophrenic patients and not to limit its use to the severely treatment-resistant patient.

Clozapine therapy has an associated sequential advantage: first, tolerability is good, and second, compliance is improved in comparison with other agents. As a result of this improved compliance, patients are less frequently rehospitalized and are therefore able to participate in long-term psychosocial rehabilitation.[16] In turn, this will lead to improvements in negative symptoms and quality of life, and that should ultimately be the objective and hope of all psychiatrists.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex), haloperidol (Haldol and others).

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